C4 36. (Amended) A pharmaceutical composition comprising the polypeptide of claim 27 together with a pharmaceutically acceptable carrier or excipient.

Please add the following claim:

C5 39. (New) The polypeptide of claim 27, wherein said homologue of SEQ ID NO:1 is encoded by a nucleic acid sequence that hybridizes under high stringency conditions to a nucleic acid sequence that encodes SEQ ID NO:1.

add D4

REMARKS

Applicant notes that in paragraph one of the restriction requirement dated April 25, 2001, the Examiner renumbered claims 28-39 as claims 27-38.

Following entry of the above amendments to the claims, claims 27-33, 36 and 39 are pending.

The amendment to claim 27 finds support in Figure 2 and on page 5, lines 6-20 of the specification.

Added claim 39 finds support on page 3, lines 6-9 of the specification.

As requested by the Examiner in paragraphs 4 and 5 of the present Office Action, the specification has been amended to insert an Abstract and to insert a sequence identifier (SEQ ID NO:1) in the description of Figure 2.

Rejection Under 35 USC § 101

Claim 27 was rejected as directed to non-statutory subject matter. Accordingly, claim 27 is amended to recite "an isolated" human spasmolytic peptide. This rejection may now be withdrawn.

Rejection Under 35 USC § 112, first paragraph

Claims 27-33 and 36 were rejected as containing "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." (page 4 of Office Action). In particular, the Examiner alleged that while the claims are genus claims directed to essentially any and all glycosylated hSPs,

> "Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the term hSP alone is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the genus". (page 5 of Office Action).

In reply, Applicants note that following the above amendments to claim 27, the claimed polypeptides now possess a common structural attribute in that they have an amino acid sequence according to SEQ ID NO:1 or a homologue thereof comprising at least six disulphide bonds that form two trefoil structures.

The presence of two trefoil domains in the claimed polypeptides provides a common structural attribute that serves to distinguished the claimed polypeptides from other polypeptides and as indicated on page 5, line 24-26, it is the trefoil domain structure encompassed by the term "homologue" in amended claim 27 that gives the claimed human spasmolytic polypeptide its biological activity (ie spasmolytic effect).

Moreover, the specification provides a representative number of "homologues" of SEQ ID NO:1 (see, for example, page 5, lines 6-20) to adequately describe the genus of polypeptides covered by claim 27.

Accordingly, since the amended claims are believed to be in compliance with the requirements of 35 USC § 112, first paragraph, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. 112, second paragraph

Claim 28 was rejected as indefinite over the recitation "Asn 15" because it is unclear if the aforementioned phrase refers to the 15th Asn in the sequence or the 15th residue from the N-terminus. In reply, Applicants submit that this rejection is rendered moot by the amendment to claim 28 presented herein.

The Examiner also rejected claims 27-33 and 36 as indefinite over the recitation "human spasmolytic polypeptide" and/or "hSP" because "the instant specification does not identify that material element or combination of elements which is unique to, and therefore definitive of 'spasmolytic polypeptide'" (page 6 of Office Action).

In reply, Applicants submit that the specification makes clear that the phrase human spasmolytic polypeptide refers to a polypeptide that has an amino acid sequence according to SEQ ID NO:1 and exhibits a spasmolytic effect (see page 2, line 22 to page 3, line 6 of the specification). Accordingly, Applicants submit that the phrase "human spasmolytic polypeptide" as used in the claims would have a clear and definite meaning to one of ordinary skill in the art.

Thus, in view of the above amendments and remarks, withdrawal of the rejections under 35 U.S.C. 112, second paragraph is respectfully requested.

Rejections Under 35 U.S.C. 103(a)

Claims 27-33 were rejected as obvious over Onda in view of Tomasetto, Alberts, Hitzeman and Lodish.

The Examiner cited to Onda as disclosing expression in yeast of a polypeptide having high homology with pancreatic spasmolytic polypeptide (PSP); Tomasetto as disclosing a cDNA encoding a protein having a putative signal sequence linked to an amino acid sequence according to SEQ ID NO:1 that contained a putative N-linked glycosylation site(Asn-X-Thr/Ser); Alberts as disclosing that most soluble proteins that are secreted are glycosylated; Hitzeman as teaching N-linked glycosylation at the sequence Asn-x-Ser/Thr; and Lodish as teaching various characteristics of the sugars found in N-linked oligosaccharides.

The Examiner therefore concluded that it would have been obvious to "express PSP in yeast, as taught by Onda, and to modify that teaching, as taught by Tomasetto, with a reasonable expectation of success." (page 9 of Office Action)

Applicants respectfully traverse this rejection.

The rejected claims are all dependent on claim 27 which is directed to a human spasmolytic polypeptide having an amino acid sequence according to SEQ ID NO:1 or a homologue thereof, where the polypeptide is in N-glycosylated form and has spasmolytic activity.

The Examiner, citing to Onda's expression in yeast of a polypeptide with high homology to PSP, suggests that one would therefore have been motivated to choose yeast as the expression system for hSP. However, it is Applicants' position that the skilled person, facing the problem of producing hSP in sufficient amounts without the improper guidance of hindsight afforded by the present application, would not have been particularly directed to select yeast as the expression system to be used for hSP production.

For example, Onda also teaches the use of non-yeast host cells, including E. coli (see page 3, line 55 of Onda), for recombinant expression of the polypeptide. In addition, in view of hSP being a relatively small and simple protein, hSP could also have been produced in large amounts by chemical polypeptide synthesis. Of course, if either chemical synthesis or expression in E. coli were used to produce hSP, glycosylated hSP would not have been produced.

Further, even assuming arguendo that expression in yeast was selected as the method of choice for producing hSP, it could not, at the priority date of the present application, be predicted that hSP would be glycosylated at Asn15. For example, Aitken et al. (Identification of Protein Consensus Sequences/ Active Site Motifs, Phosphorylation, and Other Post-translational Modifications, Ellis Horwood Limited, 1990, pages 121-123, copy attached) states that even though the sequence -Asn-Xaa-Ser/Thr- is a consensus sequence or motif for glycosylation, not every such motif is glycosylated since additional factors besides the motif (e.g., folding of the protein) can have an influence on whether glycosylation occurs. Indeed, at the time that the priority application corresponding to the present application was filed, there was no knowledge in the art that hSP might be glycosylated. Moreover, Onda's expression in yeast of a polypeptide homologous to PSP does not provide any guidance as to

whether expression in yeast of the hSP polypeptide would result in a properly folded and glycosylated hSP as Onda's polypeptide lacks the second trefoil domain present in hSP and contains no putative N-linked glycosylation site.

Finally, as shown in comparative in vivo studies of glycosylated and non-glycosylated forms of hSP [Playford et al., Gastroenterology (1995), 108(1): 108-116 copy attached], glycosylated hSP has a higher activity than non-glycosylated as determined by indomethacin-induced gastric damage (see Study 3 and Fig. 5, pages 112-113). This higher activity of the glycosylated form of hSP provides a technical advantage over the non-glycosylated form and represents a property of the glycosylated form of hSP that is neither taught nor suggested in the cited art.

Accordingly, in view of the above arguments, Applicants respectfully submit that claims 27-33 are nonobvious over the cited art.

The Examiner also rejected claims 27 and 36 as being unpatentable over Onda in view of Tomasetto, Alberts, Hitzeman and Lodish as applied to claim 27 and further in view of Turco. In particular, the Examiner alleged that it would have been obvious to make a glycosylated hSP as taught by Onda in view of Tomasetto, Alberts, Hitzeman and Lodish and to modify that teaching by making a pharmaceutical composition as taught by Turco with a reasonable expectation of success. With all due respect, Applicants disagree.

For the reasons set forth above in response to the rejection of claims 27-33, it is Applicants' position that Onda in view of Tomasetto, Alberts, Hitzeman and Lodish do not teach or suggest a glycosylated hSP. Accordingly, the combination of the aforementioned references with Turco would not render obvious the pharmaceutical composition of claim 36.

Withdrawal of this rejection is therefore respectfully requested.

Obviousness-Type Double Patenting Rejection

The Examiner rejected claims 27-33 and 36 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 and 10-13 of US Patent No. 5,783,416.

In reply, Applicants submit that they will submit an appropriate terminal disclaimer to obviate this rejection upon indication of allowable subject matter by the Examiner.

The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: October 22, 2001

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PATENT TRADEMARK OFFICE

"Marked –Up" Version Of Amendments To The Specification

Please replace the paragraph at page 11, lines 18-21 with the following:

--Fig. 2 shows the proposed structure of human spasmolytic polypeptide, HSP (SEQ. ID. NO:1). The primary amino acid sequence is taken from Tomasetto et al. [8], and the disulphide bonds are placed in homology to PSP [1].--

"Marked-Up" Version Of Amendments To The Claims

27. (Amended) An isolated human spasmolytic polypeptide [(hSP)] having an amino acid sequence according to SEQ ID NO:1

Glu Lys Pro Ser Pro Cys Gln Cys Ser Arg Leu Ser Pro His Asn Arg Thr Asn Cys Gly Phe Pro Gly Ile Thr Ser Asp Gln Cys Phe Asp Asn Gly Cys Cys Phe Asp Ser Ser Val Thr Gly Val Pro Trp Cys Phe His Pro Leu Pro Lys Gln Glu Ser Asp Gln Cys Val Met Glu Val Ser Asp Arg Arg Asn Cys Gly Tyr Pro Gly Ile Ser Pro Glu Glu Cys Ala Ser Arg Lys Cys Cys Phe Ser Asn Phe Ile Phe Glu Val Pro Trp Cys Phe Phe Pro Asn Ser Val Glu Asp Cys His Tyr

or a homologue there of comprising at least six disulphide bonds that form two trefoil domains, wherein said polypeptide is characterized by being in N-glycosylated form and having spasmolytic activity.

28. (Amended) The [hSP] polypeptide of claim [28 glycosylated is at Asn 15] 27 wherein said polypeptide is glycosylated at an Asn present at position 15 of the amino acid sequence of said polypeptide.

29. (Amended) The [hSP] polypeptide of claim [28] 27, wherein the glycosylated form comprises a glycosylated side chain comprising at least one hexose unit.

30. (Amended) The[hSP] polypeptide of claim [30] 29, wherein the glycosylated side chain comprises at least one mannose unit.

31. (Amended) The [hSP] polypeptide of claim [31] 30, wherein the glycosylated side chain comprises 13-17 mannose units.

32. (Amended) The [hSP] polypeptide of claim [28] 27, wherein the glycosylated form comprises at least one unit of N-acetyl glucosamine (GlcNAc).

33. (Amended) The [hSP] polypeptide of claim [28] 27, wherein the glycosylated form comprises $(GlcNAc)_2(Man)_{10-15}$.

36. (Amended) A pharmaceutical composition comprising the [hSP] polypeptide of claim [28] 27 together with a pharmaceutically acceptable carrier or excipient.